

10/726,148

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,  
LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005

L1 18655 S "ADAM"  
L2 23400 S DISINTEGRIN OR METALLOPROTEASE?  
L3 2132 S L1 AND L2  
L4 6866200 S CLON? OR EXPRESS? OR RECOMBINANT  
L5 1478 S L3 AND L4  
L6 94583 S PROTEOGLYCAN  
L7 42 S L5 AND L6  
L8 20 DUP REM L7 (22 DUPLICATES REMOVED)  
E YOSHIMURA K/AU  
L9 3773 S E3  
E NISHIMURA A/AU  
L10 1725 S E3  
E HIKICHI Y/AU  
L11 286 S E3  
L12 5774 S L9 OR L10 OR L11  
L13 0 S L5 AND L12  
L14 0 S L1 AND L12

=>

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February 2005

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ENTRY SESSION  
FULL ESTIMATED COST 0.06 0.27

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FILE 'LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005  
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=> s "ADAM"  
L1 18655 "ADAM"

=> s disintegrin or metalloprotease?  
L2 23400 DISINTEGRIN OR METALLOPROTEASE?

=> s l1 and l2  
L3 2132 L1 AND L2

=> s clon? or express? or recombinant  
4 FILES SEARCHED...  
L4 6866200 CLON? OR EXPRESS? OR RECOMBINANT

=> s l3 and l4

L5 1478 L3 AND L4

=> s proteoglycan  
L6 94583 PROTEOGLYCAN

=> s l5 and l6  
L7 42 L5 AND L6

=> dup rem l7  
PROCESSING COMPLETED FOR L7  
L8 20 DUP REM L7 (22 DUPLICATES REMOVED)

=> d 1-20 ibib ab

L8 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2004:546527 HCAPLUS  
DOCUMENT NUMBER: 141:99721  
TITLE: Method of modulating interaction between cell-surface  
receptor and ligand, particularly, between a  
fibroblast growth factor receptor and a neural cell  
adhesion molecule, epitope sequences, and drug  
screening uses  
INVENTOR(S): Berezin, Vladimir; Albrechtsen, Morten; Bock,  
Elisabeth  
PATENT ASSIGNEE(S): Enkam Pharmaceuticals A/S, Den.  
SOURCE: PCT Int. Appl., 154 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056865	A2	20040708	WO 2003-DK901	20031218
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			DK 2002-1982	A 20021220
			DK 2003-330	A 20030303

AB The present invention relates to a method for modulating the interaction between at least two proteins, wherein at least one of the two proteins is a functional cell-surface receptor and the other protein is the receptor ligand. The invention features a binding site of said functional cell-surface receptor on the receptor ligand and discloses a series of amino acid sequences, which are part of the structure of said binding site and/or involved in the interaction between the receptor and the ligand. Moreover, the present invention features methods for mol. design and screening of a candidate pharmaceutical compound capable of modulating the interaction between the functional cell-surface receptor and receptor ligand through the described binding site, and provides a screening assay for identification of such a compound. The invention further describes an antibody capable of binding to the above binding site and/or to an epitope comprising an amino acid sequence essential for executing the receptor ligand interaction through said binding site. The invention also concerns a variety of uses of the disclosed methods, peptide sequences and antibodies. The invention in preferred embodiments concerns the binding

site of the fibroblast growth factor receptor (FGFR) on FGFR ligands, compds. capable of modulating the receptor ligand interaction through said binding site, and antibody capable of recognition of said binding site. Drug screening methods for the manufacture of medicaments for the treatment of nervous system diseases and other disorders are claimed.

L8 ANSWER 2 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:355817 SCISEARCH

THE GENUINE ARTICLE: 810JX

TITLE: Dysregulated **expression** of adamalysin-thrombospondin genes in human breast carcinoma

AUTHOR: Porter S; Scott S D; Sassoon E M; Williams M R; Jones J L; Girling A C; Ball R Y; Edwards D R (Reprint)

CORPORATE SOURCE: Univ E Anglia, Sch Biol Sci, Norwich NR4 7TJ, Norfolk, England (Reprint); Leicester Royal Infirmary, Dept Pathol, Leicester LE2 7LX, Leics, England; Norwich Univ Hosp NHS Trust, Norwich, Norfolk, England; Dept Gen Surg, Norfolk, England; Dept Plast Surg, Norfolk, England; Dept Histopathol, Norfolk, England

COUNTRY OF AUTHOR: England

SOURCE: CLINICAL CANCER RESEARCH, (1 APR 2004) Vol. 10, No. 7, pp. 2429-2440.

Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.

ISSN: 1078-0432.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 49

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The adamalysin-thrombospondin (ADAMTS) proteinases are a relatively newly described branch of the metzincin family that contain metalloproteinase, **disintegrin**, and thrombospondin motifs. They have been implicated in various cellular events, including cleavage of **proteoglycans**, extracellular matrix degradation, inhibition of angiogenesis, gonadal development, and organogenesis. However, in many cases, their normal physiological roles and their potential for dysregulation in malignancy remain to be established. The **expression** profile of ADAMTS1-20 in human breast carcinoma was undertaken by real-time PCR using RNA isolated from malignant tumors, nonneoplastic mammary tissue, and breast cancer cell lines to identify altered regulation that may have potential pathogenetic and prognostic significance. Our studies show that seven of the ADAMTS genes (ADAMTS1, 3, 5, 8, 9, 10, and 18) are consistently down-regulated in breast carcinomas with respect to nonneoplastic mammary tissue, irrespective of the heterogeneity of the samples and the tumor type or grade (Mann-Whitney U test,  $P < 0.0001$  for each gene). Conversely, ADAMTS4, 6, 14, and 20 are consistently up-regulated in breast carcinomas ( $P = 0.005$ ,  $P < 0.0001$ ,  $P = 0.003$ , and  $P = 0.001$ , respectively). ADAMTS2, 7, 12, 13, 15, 16, 17, and 19 show no significant difference between the sample types. ADAMTS1, 2, 7, 8, 10, and 12 are **expressed** predominantly in stromal fibroblasts. ADAMTS3, 4, 5, 6, 9, and 13-20 inclusive are **expressed** predominantly in myoepithelial cells; all appear to be relatively poorly **expressed** in luminal epithelial cells. ADAMTS15 has emerged as being an independent predictor of survival, with RNA **expression** levels significantly lower ( $P = 0.007$ ) in grade 3 breast carcinoma compared with grade 1 and 2 breast carcinoma.

L8 ANSWER 3 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:257823 SCISEARCH

THE GENUINE ARTICLE: 654YF

TITLE: ADAM12/syndecan-4 signaling promotes beta(1) integrin-dependent cell spreading through protein kinase C

alpha and RhoA

AUTHOR: Thodeti C K; Albrechtsen R; Grauslund M; Asmar M; Larsson C; Takada Y; Mercurio A M; Couchman J R; Wewer U M (Reprint)

CORPORATE SOURCE: Univ Copenhagen, Inst Mol Pathol, Frederik Vs Vej 11, DK-2100 Copenhagen, Denmark (Reprint); Univ Copenhagen, Inst Mol Pathol, DK-2100 Copenhagen, Denmark; Lund Univ, Div Mol Med, SE-20502 Malmo, Sweden; Scripps Res Inst, Dept Vasc Biol VB 1, La Jolla, CA 92037 USA; Harvard Univ, Sch Med, Beth Israel Deaconess Med Ctr, Dept Pathol, Boston, MA 02215 USA; Univ London Imperial Coll Sci Technol & Med, Div Biomed Sci, London SW7 2AZ, England

COUNTRY OF AUTHOR: Denmark; Sweden; USA; England

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (14 MAR 2003) Vol. 278, No. 11, pp. 9576-9584.  
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.  
 ISSN: 0021-9258.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 66

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The ADAMs (a **disintegrin** and **metalloprotease**) comprise a large family of multidomain proteins with cell-binding and **metalloprotease** activities. The ADAM12 cysteine-rich domain (rADAM12-cys) supports cell attachment using syndecan-4 as a primary cell surface receptor that subsequently triggers beta(1) integrin-dependent cell spreading, stress fiber assembly, and focal adhesion formation. This process contrasts with cell adhesion on fibronectin, which is integrin-initiated but syndecan-4-dependent. In the present study, we investigated ADAM12/syndecan-4 signaling leading to cell spreading and stress fiber formation. We demonstrate that syndecan-4, when present in significant amounts, promotes beta(1) integrin-dependent cell spreading and stress fiber formation in response to rADAM12-cys. A mutant form of syndecan-4 deficient in protein kinase C (PKC)alpha activation or a different member of the syndecan family, syndecan-2, was unable to promote cell spreading. GF109203X and Go6976, inhibitors of PKC, completely inhibited ADAM12/syndecan-4-induced cell spreading. **Expression** of syndecan-4, but not syn4DeltaI, resulted in the accumulation of activated beta(1) integrins at the cell periphery in Chinese hamster ovary betal cells as revealed by 12G10 staining. Further, **expression** of myristoylated, constitutively active PKCalpha resulted in beta(1) integrin-dependent cell spreading, but additional activation of RhoA was required to induce stress fiber formation. In summary, these data provide novel insights into syndecan-4 signaling. Syndecan-4 can promote cell spreading in a beta(1) integrin-dependent fashion through PKCalpha and RhoA, and PKCalpha and RhoA likely function in separate pathways.

L8 ANSWER 4 OF 20 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2003223976 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12746310

TITLE: Thyroid hormone enhances aggrecanase-2/**ADAM**-TS5 **expression** and **proteoglycan** degradation in growth plate cartilage.

AUTHOR: Makihiro Seicho; Yan Weiqun; Murakami Hiroshi; Furukawa Masae; Kawai Toshihisa; Nikawa Hiroki; Yoshida Eri; Hamada Taizo; Okada Yasunori; Kato Yukio

CORPORATE SOURCE: Department of Prosthetic Dentistry, Hiroshima University Faculty of Dentistry, Minami-ku, Hiroshima 734-8553, Japan.. smakihara@forsyth.org

CONTRACT NUMBER: DE-1455 (NIDCR)

SOURCE: Endocrinology, (2003 Jun) 144 (6) 2480-8.  
 Journal code: 0375040. ISSN: 0013-7227.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200306  
 ENTRY DATE: Entered STN: 20030515  
 Last Updated on STN: 20030626  
 Entered Medline: 20030625

AB Effects of thyroid hormone on **proteoglycan** degradation in various regions of cartilage were investigated. In propylthiouracil-treated rats with hypothyroidism, **proteoglycan** degradation in epiphyseal cartilage during endochondral ossification was markedly suppressed. However, injections of T(4) reversed this effect of propylthiouracil on **proteoglycan** degradation. In pig growth plate explants, T(3) also induced breakdown of **proteoglycan**. T(3) increased the release of aggrecan monomer and core protein from the explants into the medium. Accordingly, the level of aggrecan monomer remaining in the tissue decreased after T(3) treatment, and the monomer lost hyaluronic acid-binding capacity, suggesting that the cleavage site is in the interglobular domain. The aggrecan fragment released from the T(3)-exposed explants underwent cleavage at Glu(373)-Ala(374), the major aggrecanase-cleavage site. The stimulation of **proteoglycan** degradation by T(3) was less prominent in resting cartilage explants than in growth plate explants and was barely detectable in articular cartilage explants. Using rabbit growth plate chondrocyte cultures, we explored proteases that may be involved in T(3)-induced aggrecan degradation and found that T(3) enhanced the **expression** of aggrecanase-2/**ADAM-TS5** (a **disintegrin** and a metalloproteinase domain with thrombospondin type I domains) mRNA, whereas we could not detect any enhancement of stromelysin, gelatinase, or collagenase activities or any aggrecanase-1/**ADAM-TS4** mRNA **expression**. We also found that the aggrecanase-2 mRNA level, but not aggrecanase-1, increased at the hypertrophic stage during endochondral ossification. These findings suggest that aggrecanase-2/**ADAM-TS5** is involved in aggrecan breakdown during endochondral ossification, and that thyroid hormone stimulates the aggrecan breakdown partly via the enhancement of aggrecanase-2/**ADAM-TS5**.

L8 ANSWER 5 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:946369 SCISEARCH  
 THE GENUINE ARTICLE: BX66F  
 TITLE: Use of anti-neoepitope antibodies for the analysis of degradative events in cartilage and the molecular basis for neoepitope specificity  
 AUTHOR: Mort J S (Reprint); Flannery C R; Makkerh J; Krupa J C; Lee E R  
 CORPORATE SOURCE: Shriners Hosp Children, Joint Dis Lab, 1529 Cedar Ave, Montreal, PQ H3G 1A6, Canada (Reprint); Shriners Hosp Children, Joint Dis Lab, Montreal, PQ H3G 1A6, Canada; McGill Univ, Dept Surg, Montreal, PQ H3A 2T5, Canada; Univ Cardiff, Connect Tissue Biol Lab, Cardiff Sch Biosci, Cardiff, S Glam, Wales  
 COUNTRY OF AUTHOR: Canada; Wales  
 SOURCE: PROTEASES AND THE REGULATION OF BIOLOGICAL PROCESSES, (NOV 2003) Vol. 70, pp. 107-114.  
 Publisher: PORTLAND PRESS LTD, 59 PORTLAND PL, LONDON W1N 3AJ, ENGLAND.  
 ISSN: 0067-8694.  
 DOCUMENT TYPE: Article; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 18

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Degradation of the cartilage **proteoglycan**, aggrecan, is an

essential aspect of normal growth and development, and of joint pathology. The roles of different proteolytic enzymes in this process can be determined from the sites of cleavage in the aggrecan core protein, which generates novel termini (neoepitopes). Antibodies specific for the different neoepitopes generated by such cleavage events provide powerful tools with which to analyse these processes. The same approach can be used to differentiate the processed, active forms of proteases from their inactive pro-forms. Since the proteolytic processing of these enzymes requires the removal of the inhibitory pro-region, it also results in the generation of N-terminal neoepitopes. Using the newborn rat long bone as a model system, it was shown that the active form of ADAMTS-4 [ADAM (a **disintegrin** and metalloproteinase) with thrombospondin motifs-4], but not ADAMTS-5, co-localizes with the aggrecan cleavage neoepitopes known to be produced by this metalloproteinase. Thus, in long bone growth, aggrecan turnover seems to be dependent on ADAMTS-4 activity. To demonstrate the molecular basis of the specificity of anti-neoepitope antibodies, the Fv region of a monoclonal antibody specific for a neoepitope generated by the ADAMTS-4-mediated cleavage of aggrecan has been modelled and the binding of the peptide epitope simulated. In the docked structure, the N-terminus of the peptide antigen is clearly buried in the binding-site cavity. The absence of an open cleft makes it impossible for the intact substrate to pass through the binding site, providing a rationale for the specificity of this class of antibodies.

L8 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:937303 HCAPLUS

DOCUMENT NUMBER: 138:20443

TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes

INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin

PATENT ASSIGNEE(S): Takara Bio Inc., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A 20010314
			JP 2001-74993	A 20010315
			JP 2001-102519	A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose **expression** is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17- $\beta$  estradiol (E2), were found in mice by DNA chip anal.

L8 ANSWER 7 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:710786 SCISEARCH

THE GENUINE ARTICLE: 467RY



TITLE: **ADAM**-10 protein is present in human articular cartilage primarily in the membrane-bound form and is upregulated in osteoarthritis and in response to IL-1 alpha in bovine nasal cartilage

AUTHOR: Chubinskaya S (Reprint); Mikhail R; Deutsch A; Tindal M H

CORPORATE SOURCE: Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, 1653 W Congress Pkwy, Chicago, IL 60612 USA (Reprint); Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Dept Biochem, Chicago, IL 60612 USA; Rush Med Coll, Rush Presbyterian St Lukes Med Ctr, Rheumatol Sect, Chicago, IL 60612 USA; Procter & Gamble Pharmaceut Inc, Hlth Care Res Ctr, Mason, OH USA

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF HISTOCHEMISTRY & CYTOCHEMISTRY, (SEP 2001) Vol. 49, No. 9, pp. 1165-1176.  
Publisher: HISTOCHEMICAL SOC INC, UNIV WASHINGTON, DEPT BIOSTRUCTURE, BOX 357420, SEATTLE, WA 98195 USA.  
ISSN: 0022-1554.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 32

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The objective of our study was to determine the tissue distribution and localization of **ADAM**-10 protein in human and bovine cartilage and the changes it undergoes with cartilage degeneration seen in osteoarthritis (OA) and under the influence of interleukin-1 (IL-1). Human normal and OA articular cartilage and bovine nasal cartilage cultured in the presence of IL-1 alpha were processed for histology and immunohistochemistry. **ADAM**-10 protein was extracted from human cartilage and analyzed by Western blotting using anti-**ADAM**-10 antibodies. Fluor 5 Image analyzer and Quantity One software program were applied to quantify the total amount of **ADAM**-10. **ADAM**-10 protein was detected in both human and bovine cartilage. The strongest immunostaining was found in the cytoplasm and/or cell membranes of the superficial and upper middle layer of normal adult human cartilage, in the clusters and fibrillated areas of OA cartilage, and in IL-1 alpha-stimulated bovine nasal cartilage. The distribution of **ADAM**-10 protein in bovine nasal cartilage was dependent on the length of exposure to IL-1 alpha and corresponded to the areas of **proteoglycan** depletion. By Western blotting analysis of human cartilage, **ADAM**-10 was primarily detected in the membrane-enriched fraction and its levels were increased in degenerated and OA cartilage compared to normal cartilage. The results of this study suggest that **ADAM**-10 might be an important factor associated with cartilage degenerative processes.

L8 ANSWER 8 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:313587 BIOSIS

DOCUMENT NUMBER: PREV200100313587

TITLE: RPE cells **express** several members of the metallo-**disintegrin** (**ADAM**) family of extracellular matrix modifying enzymes.

AUTHOR(S): Mckie, J. N. [Reprint author]; Bevitt, D. J. [Reprint author]; Lorite, M. J. [Reprint author]; Pimenides, D. [Reprint author]; Clarke, M. P.; Langton, K. P.; Barker, M. D.

CORPORATE SOURCE: Medical School, University of Newcastle, Newcastle Upon Tyne, UK

SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S222. print. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 29-May 04, 2001.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English  
ENTRY DATE: Entered STN: 4 Jul 2001  
Last Updated on STN: 19 Feb 2002

L8 ANSWER 9 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:365908 SCISEARCH

THE GENUINE ARTICLE: 425LD

TITLE: A **disintegrin** and **metalloprotease** with thrombospondin type1 motifs (ADAMTS-1) and IL-1 receptor type 1 mRNAs are simultaneously induced in nerve injured motor neurons

AUTHOR: Sasaki M; Seo-Kiryu S; Kato R; Kita S; Kiyama H (Reprint)

CORPORATE SOURCE: Osaka City Univ, Grad Sch Med, Dept Anat, Abeno Ku, 1-4-3 Asahimachi, Osaka 5458585, Japan (Reprint); Osaka City Univ, Grad Sch Med, Dept Anat, Abeno Ku, Osaka 5458585, Japan; Asahikawa Med Coll, Dept Oral & Maxillofacial Surg, Asahikawa, Hokkaido 0788510, Japan; Asahikawa Med Coll, Dept Anat, Asahikawa, Hokkaido 0788510, Japan

COUNTRY OF AUTHOR: Japan

SOURCE: MOLECULAR BRAIN RESEARCH, (18 APR 2001) Vol. 89, No. 1-2, pp. 158-163.

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE

AMSTERDAM, NETHERLANDS.

ISSN: 0169-328X.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 24

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Following rat hypoglossal nerve injury, **expression** of mRNAs for a **disintegrin** and **metalloprotease** with thrombospondin type 1 motifs (ADAMTS-1) and IL-1 receptor type 1 (n-1RT1) are induced in the injured motor neurons. Although N1E-115 (N1E) cells, which were treated with IL-1 alpha. showed no alteration of ADAMTS-1 mRNA **expression**, a substantial increase of ADAMTS-1 mRNA **expression** was observed in the N1E cells **expressing** IL-1RT1. These findings suggest that nerve injury promotes IL-1RT1 **expression** in the injured neurons and thereby ADAMTS-1 transcription was induced in response to IL-1 released from glial cells. (C) 2001 Elsevier Science B.V. All rights reserved.

L8 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:175926 HCAPLUS

DOCUMENT NUMBER: 132:218866

TITLE: **Cloning** of cDNA for novel human **ADAM**

family protein and its clinical use

INVENTOR(S): Yoshimura, Koji; Hikichi, Yuichi; Nishimura, Atsushi

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 109 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014227	A1	20000316	WO 1999-JP4766	19990902
W:	AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,			

	ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
CA 2341327	AA	20000316	CA 1999-2341327 19990902
AU 9954479	A1	20000327	AU 1999-54479 19990902
JP 2000139480	A2	20000523	JP 1999-248436 19990902
EP 1111047	A2	20010627	EP 1999-940629 19990902
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO		
US 6680189	B1	20040120	US 2001-786256 20010510
US 2004132157	A1	20040708	US 2003-726148 20031202
PRIORITY APPLN. INFO.:			JP 1998-250115 A 19980903
			WO 1999-JP4766 W 19990902
			US 2001-786256 A3 20010510

AB The cDNA encoding a novel protein belonging to the **ADAM** (a **disintegrin** and **metalloprotease**) family are isolated from human and its amino acid sequence deduced. The amino acid sequences deduced from **clone** pTB2052 and **clone** pTB2053 are comprised of 775 and 540 residues, resp. Methods of screening the agonists or the antagonists of protease or extracellular matrix-degrading enzyme by using the protein; prophylactics or therapeutics containing the protein for disk hernia, sciatic neuralgia, glomerulonephritis nephritis, diabetic nephropathy, hepatic fibrosis, lung fibrosis, osteopetrosis; methods of screening **proteoglycan**-degrading enzymes and their agonists or antagonists; and transgenic animals **expressing** the gene are claimed.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2000270266 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10809781

TITLE: Role of Src kinases in the **ADAM**-mediated release of L1 adhesion molecule from human tumor cells.

AUTHOR: Gutwein P; Oleszewski M; Mechtersheimer S; Agmon-Levin N; Krauss K; Altevogt P

CORPORATE SOURCE: Tumor Immunology Programme, 0710, German Cancer Research Center, D-69120 Heidelberg, Germany.

SOURCE: Journal of biological chemistry, (2000 May 19) 275 (20) 15490-7.  
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200006

ENTRY DATE: Entered STN: 20000629  
Last Updated on STN: 20000629  
Entered Medline: 20000621

AB The ectodomain of certain transmembrane molecules can be released by proteolysis, and the solubilized antigens often exert important biological functions. We demonstrated before that the L1 adhesion molecule is shed from the cell surface. Here we show that L1 release in AR breast carcinoma cells is mediated by a member of the **disintegrin** metalloproteinase (**ADAM**) family of proteinases. Up-regulation of L1 shedding by phorbol ester or pervanadate involved distinct mechanisms. Pervanadate induced shedding and rounding-up of cells from the substrate, which was blocked by the Src kinase inhibitor PP2. Tyr phosphorylation of the L1 cytoplasmic tail and the Src kinase Fyn was observed following pervanadate treatment. Up-regulation of L1 release and activation of Fyn occurred also when cells were detached by EDTA suggesting that the regulation of L1 shedding by this pathway was linked to cell morphology and adhesion. The phorbol 12-myristate 13-acetate-induced shedding was inhibited by the protein kinase C inhibitor bisindolylmaleimide I and by PD98059, a specific inhibitor of

the mitogen-activated protein kinase pathway. Soluble L1 binds to the **proteoglycan** neurocan and in bound form could support integrin-mediated cell adhesion and migration. We propose that the release of cell-associated adhesion molecules such as L1 may be relevant to promote cell migration.

L8 ANSWER 12 OF 20 MEDLINE on STN DUPLICATE 2  
ACCESSION NUMBER: 2000293210 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10831617  
TITLE: The cysteine-rich domain of human **ADAM 12** supports cell adhesion through syndecans and triggers signaling events that lead to beta1 integrin-dependent cell spreading.  
COMMENT: Comment in: J Cell Biol. 2000 May 29;149(5):995-8. PubMed ID: 10831602  
AUTHOR: Iba K; Albrechtsen R; Gilpin B; Frohlich C; Loechel F; Zolkiewska A; Ishiguro K; Kojima T; Liu W; Langford J K; Sanderson R D; Brakebusch C; Fassler R; Wewer U M  
CORPORATE SOURCE: The Institute of Molecular Pathology, University of Copenhagen, 2100 Copenhagen, Denmark.  
CONTRACT NUMBER: CA68494 (NCI)  
SOURCE: Journal of cell biology, (2000 May 29) 149 (5) 1143-56. Journal code: 0375356. ISSN: 0021-9525.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200007  
ENTRY DATE: Entered STN: 20000714  
Last Updated on STN: 20021227  
Entered Medline: 20000706

AB The **ADAMs** (a **disintegrin** and **metalloprotease**) family of proteins is involved in a variety of cellular interactions, including cell adhesion and ecto- domain shedding. Here we show that **ADAM 12** binds to cell surface syndecans. Three forms of **recombinant ADAM 12** were used in these experiments: the cysteine-rich domain made in *Escherichia coli* (rADAM 12-cys), the **disintegrin**-like and cysteine-rich domain made in insect cells (rADAM 12-DC), and full-length human **ADAM 12-S** tagged with green fluorescent protein made in mammalian cells (rADAM 12-GFP). Mesenchymal cells specifically and in a dose-dependent manner attach to **ADAM 12** via members of the syndecan family. After binding to syndecans, mesenchymal cells spread and form focal adhesions and actin stress fibers. Integrin beta1 was responsible for cell spreading because function-blocking monoclonal antibodies completely inhibited cell spreading, and chondroblasts lacking beta1 integrin attached but did not spread. These data suggest that mesenchymal cells use syndecans as the initial receptor for the **ADAM 12** cysteine-rich domain-mediated cell adhesion, and then the beta1 integrin to induce cell spreading. Interestingly, carcinoma cells attached but did not spread on **ADAM 12**. However, spreading could be efficiently induced by the addition of either 1 mM Mn(2+) or the beta1 integrin-activating monoclonal antibody 12G10, suggesting that in these carcinoma cells, the **ADAM 12-syndecan** complex fails to modulate the function of beta1 integrin.

L8 ANSWER 13 OF 20 MEDLINE on STN DUPLICATE 3  
ACCESSION NUMBER: 2000427936 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10936055  
TITLE: **ADAMTS9**, a novel member of the **ADAM-TS/ metallospodin** gene family.  
AUTHOR: Clark M E; Kelner G S; Turbeville L A; Boyer A; Arden K C; Maki R A  
CORPORATE SOURCE: Department of Molecular Biology, Neurocrine Biosciences Inc., San Diego, California 92121, USA..

mcclark@neurocrine.com  
SOURCE: Genomics, (2000 Aug 1) 67 (3) 343-50.  
Journal code: 8800135. ISSN: 0888-7543.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200009  
ENTRY DATE: Entered STN: 20000922  
Last Updated on STN: 20000922  
Entered Medline: 20000914

AB **ADAM-TS/metallospodin** genes encode a new family of proteins with structural homology to the **ADAM metalloprotease-disintegrin** family. However, unlike other **ADAMs**, these proteins contain thrombospondin type 1 (TSP1) repeats at the carboxy-terminal end and are secreted proteins instead of being membrane bound. Members of the **ADAM-TS** family have been implicated in the cleavage of **proteoglycans**, the control of organ shape during development, and the inhibition of angiogenesis. We have **cloned** a new member of the **ADAM-TS/metallospodin** family designated here as **ADAMTS9**. This protein has a **metalloprotease** domain, a **disintegrin**-like domain, one internal TSP1 motif, and three carboxy-terminal TSP1-like submotifs. In contrast to other **ADAM-TS** family members, **ADAMTS9** is **expressed** in all fetal tissues examined as well as some adult tissues. Using FISH and radiation hybrid analysis, we have localized **ADAMTS9** to chromosome 3p14.2-p14.3, an area known to be lost in hereditary renal tumors.  
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L8 ANSWER 14 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation.  
on STN

ACCESSION NUMBER: 2000:927231 SCISEARCH  
THE GENUINE ARTICLE: 379NL  
TITLE: Cellular localization of the **disintegrin** CRII-7/rMDC15 mRNA in rat PNS and CNS and regulated **expression** in postnatal development and after nerve injury  
AUTHOR: Bosse F (Reprint); Petzold G; GreinerPetter R; Pippirs U; Gillen C; Muller H W  
CORPORATE SOURCE: UNIV DUSSELDORF, DEPT NEUROL, MOL NEUROBIOL LAB, MOORENSTR 5, D-40225 DUSSELDORF, GERMANY (Reprint)  
COUNTRY OF AUTHOR: GERMANY  
SOURCE: GLIA, (DEC 2000) Vol. 32, No. 3, pp. 313-327.  
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.  
ISSN: 0894-1491.  
DOCUMENT TYPE: Article; Journal  
FILE SEGMENT: LIFE  
LANGUAGE: English  
REFERENCE COUNT: 61

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB **Disintegrins** perform putative functions in cell adhesion, signaling and fusion. We have isolated a 2815-bp rat cDNA (CRII-7) representing a transcript that is differentially **expressed** during sciatic nerve regeneration. Nucleotide sequence comparison indicates that CRII-7 is the rat homologue to the recently **cloned** cDNAs MDC15 (**ADAM** 15) and metargidin (hMDC15) of mouse and human, respectively. The CRII-7 cDNA (rMDC15) encodes a membrane-anchored glycoprotein of approximately 85 kDa containing a **disintegrin** and a **metalloprotease** domain. Cellular **metalloprotease disintegrins** are a family of proteins (**ADAMs** or MDC proteins) with important roles, e.g., in cell-cell interactions during fertilization, muscle and nerve development, or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) cleavage. Northern blot analysis demonstrated a predominant

**expression** of CRII-7/rMDC15 in the nervous system (PNS and CNS) and lung. Analysis of the CRII-7/rMDC15 transcript levels following peripheral nerve lesions demonstrated regulated mRNA **expression** during Wallerian degeneration and nerve regeneration. The steady-state levels of CRII-7/rMDC15 transcripts markedly increased within the first day after lesion and then steadily decreased for at least 4 weeks. CRII-7/rMDC15 mRNA **expression** was further examined during postnatal development and maturation of rat sciatic nerve and brain, as well as in cultured Schwann cells, meningeal fibroblasts, and astrocytes. In situ hybridization on paraffin sections showed the cellular localization of CRII-7/rMDC15 mRNA in Schwann cells and endothelial cells of peripheral nerve and in various neuronal populations in brain and spinal cord. (C) 2000 Wiley-Liss, Inc.

L8 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:428698 HCAPLUS  
DOCUMENT NUMBER: 134:112014  
TITLE: New metalloproteinase family, ADAMTS  
AUTHOR(S): Kuno, Kouji  
CORPORATE SOURCE: Cancer Res. Inst., Kanazawa Univ., Japan  
SOURCE: Immunology Frontier (2000), 10(3), 159-166  
CODEN: IMFREG; ISSN: 0917-0774  
PUBLISHER: Medikaru Rebyusha  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: Japanese

AB A review with 15 refs. on the structure and organ distribution of the ADAMTS family of metalloproteinases. **ADAM** (a **disintegrin** and metalloproteinase) family are the membranous protease participating in shedding of various mols.; ADAM17 is the tumor necrosis factor  $\alpha$  converting enzyme (TACE). ADAMTS ( **ADAM** family gene with thrombospondin motif) family are secretory proteases with thrombospondin (TSP) type 1 motif. ADAMTS-1 binds the extracellular matrix (ECM) by 3 TSP type 1 motives and spacer regions. ADAMTS-1 is **expressed** in various organs, and plays important role in formation and function of renal pelvis tissue. Anomaly in type I procollagen N-protease (pNP1, ADAMTS-2) causes disorder in dermal tissue in human Ehlers-Danlos syndrome type VIIC. Aggricase in ADAMTS family participates in degradation of cartilage **proteoglycan** in chronic rheumatoid arthritis and osteoarthritis, and it may be the therapeutic target.

L8 ANSWER 16 OF 20 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 1999263385 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10329602  
TITLE: Cysteine-rich domain of human **ADAM** 12 (meltrin alpha) supports tumor cell adhesion.  
AUTHOR: Iba K; Albrechtsen R; Gilpin B J; Loechel F; Wewer U M  
CORPORATE SOURCE: Institute of Molecular Pathology, University of Copenhagen, Copenhagen, Denmark.  
SOURCE: American journal of pathology, (1999 May) 154 (5) 1489-501.  
Journal code: 0370502. ISSN: 0002-9440.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199906  
ENTRY DATE: Entered STN: 19990614  
Last Updated on STN: 20030128  
Entered Medline: 19990603

AB The **ADAMs** (A **disintegrin** and metalloprotease ) comprise a family of membrane-anchored cell surface proteins with a putative role in cell-cell and/or cell-matrix interactions. By immunostaining, **ADAM** 12 (meltrin alpha) was up-regulated in several human carcinomas and could be detected along the tumor cell membranes. Because of this intriguing staining pattern, we investigated



the early stages of cartilage destruction that lead to surface fibrillation. However, MMPs may be involved in later stages where collagen degradation is prevalent. The role that **ADAMs** play is still unknown, although they are postulated to play an important role in shedding or activation of different classes of matrix proteases. Furthermore, we have observed changes in the patterns of cartilage **expression** in fresh tissue and model culture systems. This work has indicated clearly that there are several different classes of enzyme that can be targeted for innovative therapies which could slow or halt cartilage destruction in arthritis.

L8 ANSWER 18 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN DUPLICATE 6

ACCESSION NUMBER: 1999263307 EMBASE  
TITLE: **Expression** of ADAMTS homologues in articular cartilage.  
AUTHOR: Flannery C.R.; Little C.B.; Hughes C.E.; Caterson B.  
CORPORATE SOURCE: C.R. Flannery, Connective Tissue Biology Lab., Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF1 3US, United Kingdom. FlanneryCR@Cardiff.ac.uk  
SOURCE: Biochemical and Biophysical Research Communications, (5 Jul 1999) 260/2 (318-322).  
Refs: 22  
ISSN: 0006-291X CODEN: BBRCA  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
029 Clinical Biochemistry  
033 Orthopedic Surgery  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Articular chondrocytes possess the capacity to **express** a number of **ADAM** (A **Disintegrin** And Metalloproteinase) family members, thereby implicating a role for such proteins in the turnover of cartilage extracellular matrix molecules. Recently, the sequence for the human orthologue of an 'aggrecanase' isolated from bovine nasal cartilage has been elucidated, and the **recombinant** protein product shown to be capable of cleaving aggrecan specifically at the relevant peptide bonds which are hydrolyzed in situ during cartilage degradation. The sequence for the human 'aggrecanase' exhibits homology with that of murine ADAMTS-1, an **ADAM** with thrombospondin type I motifs. In the present study we have identified additional ADAMTS homologues and have examined their mRNA **expression** profiles in freshly excised human articular cartilage and in human cartilage explant cultures stimulated with IL-1, TNF- $\alpha$ , or retinoic acid, agents which enhance 'aggrecanase' activity in vitro. Significantly, cartilage exposed to retinoic acid showed a marked increase in the release of 'aggrecanase'-generated aggrecan catabolites with no concomitant increase in mRNA levels for any of the ADAMTS homologues investigated. These findings indicate that enhanced 'aggrecanase' activity, which may be attributed to known ADAMTS homologues, may be predominantly regulated by post-transcriptional mechanism(s), and may raise the possibility for the existence of other as yet unidentified 'aggrecanase(s)'.

L8 ANSWER 19 OF 20 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 1999357011 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10429942  
TITLE: Effects of culture conditions and exposure to catabolic stimulators (IL-1 and retinoic acid) on the **expression** of matrix metalloproteinases (MMPs) and **disintegrin** metalloproteinases (**ADAMs**) by articular cartilage chondrocytes.  
AUTHOR: Flannery C R; Little C B; Caterson B; Hughes C E  
CORPORATE SOURCE: Connective Tissue Biology Laboratories, Cardiff School of



Biosciences, Cardiff University, Wales, UK..  
flannerycr@cardiff.ac.uk

SOURCE: Matrix biology : journal of the International Society for  
Matrix Biology, (1999 Jun) 18 (3) 225-37.  
Journal code: 9432592. ISSN: 0945-053X.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-AF069641; GENBANK-AF069642; GENBANK-AF069643;  
GENBANK-AF069644; GENBANK-AF069645; GENBANK-AF069646;  
GENBANK-AF069647; GENBANK-AF069648; GENBANK-AF069649  
ENTRY MONTH: 199910  
ENTRY DATE: Entered STN: 20000111  
Last Updated on STN: 20000111  
Entered Medline: 19991026

AB The chondrocytes of articular cartilage synthesize a number of proteinases which are capable of degrading the component molecules of this specialized extracellular matrix. The use of class-specific proteinase inhibitors indicates that major activities responsible for catabolism of **proteoglycan** (aggrecan) and collagen are attributable to zinc-dependent metalloproteinases. In this study, we have compared the mRNA **expression** profiles of two matrix metalloproteinases (MMP-3 and MMP-13) and five **disintegrin**-metalloproteinases (**ADAM**-10, **ADAM**-9, **ADAM**-15, TNF-alpha-converting enzyme and decysin) by chondrocytes (human, porcine and bovine) from fresh cartilage and in cartilage explant cultures and isolated cells cultured in monolayer or in agarose gels. Such cultures were maintained in the presence or absence of interleukin-1 (IL-1) or all-trans-retinoic acid, two agents which promote cartilage matrix degradation in vitro. Whereas transcripts for all metalloproteinases examined were detected in chondrocytes from human osteoarthritic cartilage in monolayer cultures, mRNAs for **ADAM**-15 and decysin were not present in fresh osteoarthritic human cartilage or explant cultures. Similarly, **expression** of porcine and bovine metalloproteinase mRNAs varied with different culture conditions. Novel cDNA sequences obtained for porcine and bovine MMP-3 and MMP-13, porcine **ADAM**-10, porcine and bovine **ADAM**-9 and porcine TACE confirmed **expression** of mRNAs for these molecules by articular chondrocytes. Quantitative RT-PCR analysis was used to determine the effects of IL-1 and retinoic acid on metalloproteinase mRNA levels in human chondrocytes cultured in monolayer and in porcine chondrocytes cultured in agarose. For the MMPs, IL-1 treatment resulted in an approximately two to threefold increase in human and porcine MMP-3 and MMP-13 mRNAs, while retinoic acid treatment caused a statistically significant increase in human MMP-3 mRNA levels, but no significant change in transcript levels for porcine MMP-3 nor human or porcine MMP-13. The mRNA levels for **ADAM**-15 were elevated in human monolayer chondrocytes exposed to IL-1 or retinoic acid, while transcripts levels for TNF-alpha converting enzyme were increased in response to retinoic acid. In contrast, **ADAM**-9 mRNA levels were decreased in human monolayer chondrocytes exposed to IL-1 or retinoic acid. The results demonstrate that chondrocyte metalloproteinase **expression** can vary dependent on cell environment in situ and in vitro, and information on chondrocyte MMP and **ADAM** gene **expression** following cytokine (IL-1) or retinoid stimulation.

L8 ANSWER 20 OF 20 MEDLINE on STN

ACCESSION NUMBER: 1998157987 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9488721

TITLE: The interglobular domain of cartilage aggrecan is cleaved by hemorrhagic metalloproteinase HT-d (atrolysin C) at the matrix metalloproteinase and aggrecanase sites.

AUTHOR: Tortorella M D; Pratta M A; Fox J W; Arner E C  
CORPORATE SOURCE: Inflammatory Diseases Research, The DuPont Merck

SOURCE: Pharmaceutical Company, Wilmington, Delaware 19880, USA.  
 Journal of biological chemistry, (1998 Mar 6) 273 (10)  
 5846-50.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199804  
 ENTRY DATE: Entered STN: 19980416  
 Last Updated on STN: 20000303  
 Entered Medline: 19980407

AB Two primary cleavage sites have been identified within the interglobular domain of the cartilage aggrecan core protein: one is between amino acid residues Asn 341 and Phe342, where many matrix metalloproteinases (MMP) have been shown to cleave; and the other is between amino acid residues Glu373 and Ala374. Although cleavage at the Glu373-Ala374 site is believed to play a critical role in cartilage aggrecan degradation in arthritic diseases, the enzyme responsible for cleavage at this site, "aggrecanase," has not been identified. Members of the ADAM (a disintegrin and metalloproteinase) family of proteins, which shows structural homology to the snake venom hemorrhagic metalloproteinases (reprolysins), have recently been demonstrated to be **expressed** in articular chondrocytes. Because many ADAM family members have a putative proteinase function, this raises the possibility that aggrecanase may be a member of this family of proteases. To examine whether reprolysins have the ability to cleave aggrecan at either the aggrecanase site or the MMP site, the snake venom hemorrhagic toxin metalloproteinase HT-d (atrolysin C) was tested for its ability to cleave bovine aggrecan monomer. Cleavage was monitored using the BC-3 antibody, which recognizes aggrecan fragments with the new NH2 terminus ARGSV generated by cleavage at the aggrecanase site, and with the AF-28 antibody, which recognizes aggrecan fragments with the new NH2 terminus FFGVG generated by cleavage at the MMP site. Cleavage at both the aggrecanase and MMP sites occurred in a concentration-dependent manner with 100 nM atrolysin C or greater. AF-28-reactive fragments were generated by 30 min of incubation, and levels were maximal by 8 h; BC-3-reactive fragments were detected at 2 h and continued to increase through 48 h, thus suggesting that atrolysin C can cleave at the MMP and aggrecanase sites. NH2-terminal aggrecan fragments generated by cleavage at the aggrecanase site were also detected using antisera recognizing the new COOH terminus, NITEGE, formed by cleavage at the Glu373-Ala374 bond, indicating that cleavage at this site does not require prior cleavage at the MMP site. These data provide the first demonstration that a reprolysin can cleave the core protein of aggrecan and the first example of a specific protease that can cleave at the aggrecanase site independent of cleavage at the MMP cleavage site.

=> e yoshimura k/au

E1	1	YOSHIMURA JYUN YA/AU
E2	2	YOSHIMURA JYUNICHI/AU
E3	3773 --->	YOSHIMURA K/AU
E4	2	YOSHIMURA K */AU
E5	2	YOSHIMURA K I/AU
E6	1	YOSHIMURA K O H/AU
E7	1	YOSHIMURA KAICHI/AU
E8	9	YOSHIMURA KAN/AU
E9	1	YOSHIMURA KANICHI/AU
E10	26	YOSHIMURA KANJI/AU
E11	1	YOSHIMURA KAORI/AU
E12	7	YOSHIMURA KAORU/AU

=> s e3

L9 3773 "YOSHIMURA K"/AU

=> e nishimura a/au

E1	1	NISHIMUR YOSHIKI/AU
E2	13	NISHIMURA/AU
E3	1725	--> NISHIMURA A/AU
E4	3	NISHIMURA A A/AU
E5	1	NISHIMURA A H/AU
E6	32	NISHIMURA A L/AU
E7	101	NISHIMURA A M/AU
E8	1	NISHIMURA ABE A/AU
E9	1	NISHIMURA AGNES/AU
E10	7	NISHIMURA AGNES L/AU
E11	2	NISHIMURA AKANE M/AU
E12	7	NISHIMURA AKEMI/AU

=> s e3

L10 1725 "NISHIMURA A"/AU

=> e hikichi y/au

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E4	63	HIKICHI YASUFUMI/AU
E5	119	HIKICHI YASUO/AU
E6	1	HIKICHI YASUSHI/AU
E7	29	HIKICHI YOSHINAO/AU
E8	2	HIKICHI YOSHIYUKI/AU
E9	20	HIKICHI YUICHI/AU
E10	2	HIKICHI YUKA/AU
E11	18	HIKICHI YUKIKO/AU
E12	1	HIKICHI YUKIYOSHI/AU

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L11 286 "HIKICHI Y"/AU

=> s l9 or l10 or l11

L12 5774 L9 OR L10 OR L11

=> d his

(FILE 'HOME' ENTERED AT 08:49:16 ON 11 JAN 2005)

FILE 'STNGUIDE' ENTERED AT 08:49:22 ON 11 JAN 2005

FILE 'HOME' ENTERED AT 08:49:28 ON 11 JAN 2005

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005

L1	18655	S "ADAM"
L2	23400	S DISINTEGRIN OR METALLOPROTEASE?
L3	2132	S L1 AND L2
L4	6866200	S CLON? OR EXPRESS? OR RECOMBINANT
L5	1478	S L3 AND L4
L6	94583	S PROTEOGLYCAN
L7	42	S L5 AND L6
L8	20	DUP REM L7 (22 DUPLICATES REMOVED)
		E YOSHIMURA K/AU
L9	3773	S E3
		E NISHIMURA A/AU
L10	1725	S E3
		E HIKICHI Y/AU
L11	286	S E3
L12	5774	S L9 OR L10 OR L11

=> s l5 and l12  
L13           0 L5 AND L12

=> s l1 and l12  
L14           0 L1 AND L12

=> d his

(FILE 'HOME' ENTERED AT 08:49:16 ON 11 JAN 2005)

FILE 'STNGUIDE' ENTERED AT 08:49:22 ON 11 JAN 2005

FILE 'HOME' ENTERED AT 08:49:28 ON 11 JAN 2005

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 08:49:56 ON 11 JAN 2005

L1           18655 S "ADAM"  
L2           23400 S DISINTEGRIN OR METALLOPROTEASE?  
L3           2132 S L1 AND L2  
L4           6866200 S CLON? OR EXPRESS? OR RECOMBINANT  
L5           1478 S L3 AND L4  
L6           94583 S PROTEOGLYCAN  
L7           42 S L5 AND L6  
L8           20 DUP REM L7 (22 DUPLICATES REMOVED)  
              E YOSHIMURA K/AU  
L9           3773 S E3  
              E NISHIMURA A/AU  
L10          1725 S E3  
              E HIKICHI Y/AU  
L11          286 S E3  
L12          5774 S L9 OR L10 OR L11  
L13          0 S L5 AND L12  
L14          0 S L1 AND L12

	Issue Date	Pages	Document ID	Title
1	20041223	82	US 20040259896 A1	Aza spiro alkane derivatives as inhibitors of metalloproteases
2	20040513	115	US 20040091962 A1	Proteases
3	20040429	67	US 20040081971 A1	Protein modification and maintenance molecules
4	20040429	95	US 20040081961 A1	Proteases
5	20040422	108	US 20040077048 A1	Protein modification and maintenance molecules
6	20040318	105	US 20040053269 A1	Proteases
7	20040212	106	US 20040029249 A1	Proteases
8	20040205	118	US 20040023243 A1	Proteases
9	20031218	121	US 20030232349 A1	Proteases
10	20030904	40	US 20030166899 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
11	20030814	278	US 20030154032 A1	Methods and compositions for diagnosing and treating rheumatoid arthritis
12	20030703	81	US 20030124706 A1	Proteases
13	20030703	64	US 20030124579 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer

	Issue Date	Pages	Document ID	Title
14	20020808	48	US 20020107361 A1	Novel metalloproteases having thrombospondin domains and nucleic acid compositions encoding the same
15	20020711	43	US 20020090373 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
16	20011206	31	US 20010049106 A1	ADAMTS polypeptides, nucleic acids encoding them, and uses thereof
17	20040120	51	US 6680189 B1	Protein and DNA thereof

	Issue Date	Pages	Document ID	Title
1	20041216	84	US 20040253602 A1	Therapeutic and diagnostic methods and compositions based on jagged/notch proteins and nucleic acids
2	20041125	104	US 20040235071 A1	Methods and compositions for treating cancer using 15986, 2188, 20743, 9148, 9151, 9791, 44252, 14184, 42461, 8204, 7970, 25552, 21657, 26492, 2411, 15088, 1905, 28899, 63380, 33935, 10480, 12686, 25501, 17694, 15701, 53062, 49908, 21612, 38949, 6216, 46863, 9235, 2201, 6985, 9883, 12238, 18057, 21617, 39228, 49928, 54476, 62113, 64316, 12264, 32362, 58198, 2887, 3205, 8557, 9600, 9693, 44867, 53058, 55556, 57658, 2208, 10252, 10302, 14218, 33877, 10317, 10485, 25964, 14815, 1363, 1397, 14827, 21708, 3801, 64698, 2179 or 13249
3	20041111	65	US 20040224378 A1	Methods for using ADAMTS-12, an integrin and metalloprotease with thrombspondin motifs
4	20041021	45	US 20040209799 A1	JAK/STAT pathway inhibitors and the uses thereof
5	20040916	35	US 20040180417 A1	Secretase/sheddase with asp-ase activity on the beta-site app-cleaving enzyme (bace, asp2, memepsin2)
6	20040708	56	US 20040132157 A1	Novel protein and DNA thereof

	Issue Date	Pages	Document ID	Title
7	20040624	217	US 20040121349 A1	Novel 27877, 18080, 14081, 32140, 50352, 16658, 14223, 16002, 50566, 65552 and 65577 molecules and uses therefor
8	20040304	32	US 20040043387 A1	Nucleic acid molecules and polypeptides related to h-ADAM7
9	20040304	207	US 20040043021 A1	Nucleotide and amino acid sequences relating to respiratory diseases and obesity
10	20040205	485	US 20040023215 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
11	20040108	245	US 20040006016 A1	Novel 27875, 22025, 27420, 17906, 16319, 55092 and 10218 molecules and uses therefor
12	20040101	441	US 20040002470 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
13	20031113	196	US 20030212256 A1	Proteins and nucleic acids encoding same



	Issue Date	Pages	Document ID	Title
14	20030821	80	US 20030157082 A1	Methods and compositions for treating cancer using 140, 1470, 1686, 2089, 2427, 3702, 5891, 6428, 7181, 7660, 25641, 69583, 49863, 8897, 1682, 17667, 9235, 3703, 14171, 10359, 1660, 1450, 18894, 2088, 32427, 2160, 9252, 9389, 1642, 85269, 10297, 1584, 9525, 14124, 4469, 8990, 2100, 9288, 64698, 10480, 20893, 33230, 1586, 9943, 16334, 68862, 9011, 14031, 6178, 21225, 1420, 32236, 2099, 2150, 26583, 2784, 8941, 9811, 27444, 50566 or 66428 molecules
15	20030814	127	US 20030153018 A1	Methods and compositions for treating cancer using 2192, 2193, 6568, 8895, 9138, 9217, 9609, 9857, 9882, 10025, 20657, 21163, 25848, 25968, 32603, 32670, 33794, 54476 and 94710
16	20030807	38	US 20030148410 A1	Novel genes, compositions, kits, and methods for identification, assessment, prevention, and therapy of colon cancer
17	20030724	417	US 20030138925 A1	Novel human gene relating to respiratory diseases, obesity, and inflammatory bowel disease
18	20030417	111	US 20030073622 A1	Novel proteins and nucleic acids encoding same

	Issue Date	Pages	Document ID	Title
19	20030123	71	US 20030017572 A1	56294 and 56629, novel human metalloproteases and uses thereof
20	20021219	100	US 20020192748 A1	Novel polynucleotides and polypeptides encoded thereby
21	20020829	71	US 20020119555 A1	53014, a human metalloprotease family member and uses therefor
22	20020620	55	US 20020076778 A1	33428, a novel human metalloprotease family member and uses thereof
23	20020613	67	US 20020072490 A1	33428, a novel human metalloprotease family member and uses thereof
24	20040406	79	US 6716974 B1	Therapeutic and diagnostic methods and compositions based on jagged/notch proteins and nucleic acids
25	20040120	51	US 6680189 B1	Protein and DNA thereof

	<b>L #</b>	<b>Hits</b>	<b>Search Text</b>
1	L1	15150	"ADAM"
2	L2	3873	disintegrin or metalloprotease\$2
3	L3	417	l1 same l2
4	L4	69459 5	clon\$3 or express\$3 or recombinant
5	L5	187	l3 same l4
6	L6	5637	proteoglycan
7	L7	17	l5 same l6
8	L8	26365	YOSHIMURA NISHIMURA HIKICHI
9	L9	25	l3 and l8